REMARKS

The Applicants have amended claims 55 and 70 to indicate that the liposomes have "empty aqueous cores," and to include the term "Gaussian distribution" in claim 55 in accordance with the Examiner's suggestions. The term "empty aqueous cores" means that the aqueous cores are free of drug but does not mean that the aqueous cores are free of non-drug materials such as water and other molecules. Claims 57, 58, 72, and 73 were amended to clarify that the "therapeutically effective amount" is based on body weight. The cancellation of claims 61 and 76 were made for the purpose of pursuing such canceled subject matter in related applications at the option of the Applicants and not for patentability. The Applicants expressly reserve the right to prosecute any unclaimed or canceled subject matter in the present application or in any related application.

The amended claims are fully supported by the specification and the originally filed claims, and do not constitute new matter. Specifically, the recitation of "having empty aqueous cores" in the claims is supported by the specification at p. 7, *l.* 37 to p. 8, *l.* 1 (disclosing liposomes as structures having lipid-containing membranes enclosing an aqueous interior).

In addition, the term "having a Gaussian distribution wherein at least about 68% of the liposomes have a mean diameter of 125 ± 30 nm" is supported by the specification at p. 17, *ll.* 8-23 which describes the preparation and use of a population of liposomes having a diameter of 125 nm plus or minus 30 nm as measured by QELS (Quasi-Electric-Light-Scattering) analysis, utilizing a Nicomp Model 370 submicron laser particle sizer (Pacific Scientific, MD) equipped with a 5-mW He-Ne Laser. As explained in the specification, the Nicomp QELS system used to characterize the liposome population analyzes fluctuations in light-scattering intensities due to liposome diffusion in solution. *Id.* The measured diffusion coefficient is used to obtain the average hydrodynamic radius (*see* specification at p. 17, *ll.* 13-15) and the mean diameter of liposomes is expressed as the mean plus or minus 1 standard deviation (125 ± 30 nm) (*see* specification at p. 78, *ll.* 15-23), arrived at using a Gaussian analysis (*see, The Nicomp 370 Model Submicron Particle Sizer User Manual* at pp. 24-25, entitled, "The Simplest Approach to Size Distributions: Gaussian Analysis," previously submitted as Exhibit B in Applicant's Reply filed on May 2, 2003).

1. The Obviousness-Type Double Patenting Rejection Should Be Withdrawn

The Examiner has rejected claims 55-84 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,139,871. The Applicants respectfully traverse this rejection in view of the amendments made herein. Alternatively, the Applicants request that the Examiner continue to maintain this rejection in abeyance until the claims are otherwise deemed allowable.

2. The Rejections Under 35 U.S.C. § 102 Should Be Withdrawn

A. The Claims are Patentable Over Liu

Claims 55-56, 60-61, 67-71, 75, 76, and 82-84 are rejected under 35 U.S.C. § 102(b) as being anticipated by Liu. According to the Examiner, Liu discloses liposomes having sizes falling within the range claimed by the Applicants (noting the abstract, materials & methods and results of Liu). The Examiner states that the Applicant's arguments were considered but not found to be persuasive because: (1) Liu teaches liposomes even without radioactive tracer and therefore the composition appears to be pharmaceutically acceptable; (2) Applicant has not shown that the amounts in Liu are not therapeutically effective- *i.e.*, that Liu's compositions do not remove cholesterol; and (3) Liu teaches liposomes of 120 nm despite the argument that sonication will produce liposomes in the 25-50 nm range.

With respect to (1) above, the Applicant's respectfully note that Liu does not teach pharmaceutically acceptable liposomes (*see* p. 349 of Liu under the heading entitled "Materials and Methods" and subheading entitled, "Liposome preparation"). Accordingly, the Examiner has failed to show where in Liu, it discloses pharmaceutically acceptable liposomes for the treatment of atherosclerosis, hyperlipidemia, or hypoalphalipoproteinemia. With respect to (2) above, the Examiner has failed to show that Liu's liposomes are therapeutically effective. The Applicants respectfully request that the Examiner show (by page and line number) exactly where in Liu it teaches either pharmaceutically acceptable or therapeutically effective amounts of liposomes for the treatment of atherosclerosis, hyperlipidemia, and hypoalphalipoproteinemia, or otherwise withdraw the rejection. Applicants respectfully note that the burden is on the Examiner to show that the reference discloses all of the claim limitations (the burden is not on the Applicant to establish a negative (*see* MPEP 2131).

Moreover, with respect to (3) above, Liu does not teach liposomes of 120 nm. Rather Liu teaches a range where the diameter (d) $\leqq 120$ (p. 350, *l.* 20) and where d $\leqq 200$ (p. 1, col. 2, *l.* 8). The claimed invention requires a population of liposomes that has a "Gaussian distribution" wherein at least 68% of the liposomes have a mean diameter of about 125 ± 30 nm. Liu does not teach such a population of liposomes. Moreover, given their size range, the liposomes of Liu would not behave the same as those claimed.

Indeed, the Examiner has failed to show where Liu teaches a population of liposomes having the claimed Gaussian distribution which "mobilize more cholesterol than an equal amount of unilamellar phospholipid liposomes having a mean diameter of 30 ± 7 nm as measured in mice. Liu does not teach this claim limitation. Likewise, the Examiner has failed to show where Liu teaches liposomes with a Gaussian distribution that are effective in promoting cholesterol efflux without causing a substantial increase in LDL or esterified cholesterol levels. In sum, Liu fails to disclose several claim elements namely, empty

liposomes of the claimed population having the claimed benefit. Accordingly, Liu cannot, either expressly or inherently, anticipate the claims under 35 U.S.C. § 102(b). The rejection should be withdrawn.

B. The Claims Are Patentable Over Hager

Claims 55-56, 60, 62, 64-68, 70-71, 75, 77, and 79-83 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hager (EP 0470437). According to the Examiner, Hager discloses liposomes having an average diameter of 100 nm containing phophatidylcholine for the treatment of atherosclerosis (noting pages 1-11, 15-16 of the English translation). The Examiner states that the Applicant's arguments were considered but not found to be persuasive because: (1) the Gaussian distribution argument by Applicant is not recited as a limitation in the claim and (2) the inclusion of propidium iodide does not necessarily mean that Hager's liposomes are not pharmaceutically acceptable since many DNA alkylating agents (although toxic, mutagenic, and carcinogenic) are used in cancer therapy in humans; and (3) one of ordinary skill in the art will not attach the marker if the desired goal is only to treat atherosclerosis in humans and not for diagnostic purposes since the reference through examples shows how to make liposomes of different sizes.

With respect to (1) and (3), the Applicants have amended claims 55-69 to clarify that the liposomes have "a Gaussian distribution" wherein at least 68% of the liposomes have a mean diameter of about 125 ± 30 nm. Hager does not teach this limitation. In addition, the Examiner has failed to show where Hager teaches that its liposomes "mobilize more cholesterol than an equal amount of unilamellar phospholipid liposomes having a mean diameter of 30 ± 7 nm as measured in mice. Furthermore, the Examiner has failed to show that Hager teaches the limitation of claims 70-84 wherein the liposomes are effective in promoting cholesterol efflux without causing a substantial increase in LDL or esterified cholesterol levels.

With respect to (2), please see Exhibit E of Applicant's previous Reply filed on May 2, 2003 which contains a Material Data Safety Sheet on propidium iodide from Sigma-Aldrich Corporation showing that propidium iodide is not pharmaceutically acceptable. In addition, the Applicants respectfully note that the claims recite a composition for the treatment of atherosclerosis, hyperlipidemia, or hypoalphalipoproteinemia (not cancer) such that even if propidium iodide were a DNA alkylating agent the claim would be novel. However, the Examiner has provided no evidence that propidium iodide is a DNA alkylating agent.

Thus, Hager does not teach each and every element of the claims, either expressly or inherently, and therefore does not anticipate the claims under 35 U.S.C. § 102(b).

3. The Rejections Under 35 U.S.C. § 103 Should Be Withdrawn

A. The Claims Are Patentable Over Hager by Itself or in View of Williams 1986

Claims 55-84 are rejected under 35 U.S.C. § 103 as being unpatentable over Hager by itself or in View of Williams 1986. According to the Examiner, although the Applicant argues that the claims are limited to a particular Gaussian distribution, the Examiner asserts that the instant claims do not recite such a limitation. In response, the Applicants have amended claims 55-69 to clarify that the liposomes have "a Gaussian distribution" wherein "at least 68% of the liposomes have a mean diameter of about 125 ± 30 nm, which liposomes mobilize more cholesterol than an equal amount of unilamellar phospholipid liposomes having a mean diameter of 30 ± 7 nm as measured in mice." Neither Hager or Williams teaches or suggests these limitations. Likewise the Examiner has failed to show where Hager or Williams teaches or suggests the population of liposomes of claims 70-84 wherein the liposomes are effective in promoting cholesterol efflux without causing a substantial increase in LDL or esterified cholesterol levels. See MPEP 2143.03 (a *prima facie* case of obviousness requires that all of the claim limitations be taught or suggested by the prior art).

In addition, a finding of obviousness requires that the prior art both suggest the invention and provide one of ordinary skill with a reasonable expectation of success. *In re O'Farrell* 853 F2d 894, 903, 7 USPQ2d 1673 (Fed. Cir. 1988). Secondary considerations such as unexpected results must be considered if present. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538-39, 218 USPQ 871, 879 (Fed. Cir. 1983); *In re Merck & Co., Inc.*, 800 F.2d 1091, 1096, 231 USPQ 375, 378 (Fed. Cir. 1986). Here, the Applicant's population of liposomes having the claimed Gaussian distribution is not suggested by the prior art and achieves unexpected results.

Applicant's unexpected results lie in the discovery that liposomes having the claimed Gaussian distribution wherein at least 68% of the liposomes have a mean diameter of 125 ± 30 nm: (1) do not substantially raise LDL or esterified cholesterol levels; and (2) mobilize more cholesterol from peripheral tissues (such as atherosclerotic plaques) than an equivalent amount (per weight) of liposomes having a different Gaussian distribution with smaller liposomes (*see* specification at p. 8, *ll.* 7-18; p. 15, *ll.* 21-22; p. 20, *l.* 20 to p. 22, *l.* 21; p. 32, *l.* 25 to p. 33, *l.* 32; and Figures, 2A, 2B, and 4B). Neither Hager or Williams teach or suggest a population of liposomes having the claimed Gaussian distribution, or a population of liposomes that do not substantially raise LDL (or esterified) cholesterol levels, or a population of liposomes that optimally mobilizes cholesterol from peripheral tissue. Thus, Applicants respectfully request that the rejection under 35 U.S.C. § 103 as being unpatentable over Hager by itself or in view of Williams 1986 be withdrawn.

B. The Claims Are Patentable Over Williams (1984 or 1986) in view of Liu

Claims 55-84 are rejected under 35 U.S.C. § 103 as being unpatentable over Williams (1984 or 1986) in view of Liu. In response, the Applicants have amended claims 55-69 to clarify that the liposomes have "a Gaussian distribution wherein at least 68% of the liposomes have a mean diameter of about 125 ± 30 nm." Neither Williams (1984 or 1986) or Liu teaches or suggests this limitation. Nor does Williams (1984 or 1986) or Liu teach or suggest a population of liposomes having the claimed Gaussian distribution which mobilize "more cholesterol than an equal amount of unilamellar phospholipid liposomes having a mean diameter of 30 ± 7 nm as measured in mice." Furthermore, the Examiner has failed to show where Williams (1984 or 1986) or Liu teaches or suggests the limitation in claims 70-84 which requires that the liposomes be effective in promoting cholesterol efflux without causing a substantial increase in LDL or esterified cholesterol levels. See MPEP 2143.03 (a *prima facie* case of obviousness requires that all of the claim limitations be taught or suggested by the prior art).

Williams 1984 discloses liposomes with sizes between 21-50 nm and 30-60 nm (p. 419, lines 22-23; p.422, lines 43-45). Similarly, Williams 1986 describes the preparation of SUVs[1] and the uptake of endogenous cholesterol when the SUVs are administered to dogs. The data presented in Williams 1986 shows that 4 hours after infusion with SUVs a dramatic increase in LDL occurs as a result of this treatment (*see* Williams 1986, Fig. 2A, the peak labeled "P1" [LDL] at four hours ["t = 4h"]). Thus, Williams 1986 not only discloses liposomes that are smaller than those presently claimed but the reference actually **teaches away** from the presently claimed invention because it shows an increase in esterified cholesterol and LDL after administration. Williams 1984 or 1986 do not cure the deficiencies of Liu, or vice versa.

Accordingly, the rejection under 35 USC 103(a) as being unpatentable over Williams (1984 or 1986) in view of Liu should be withdrawn.

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[1] In Williams 1986, the phospholipid dispersion was prepared using ultrasonic irradiation (with a titanium probe) for a total of 40 minutes, followed by ultracentrifugation for 1 hour at 100,000 x g to remove fragments of titanium shed by the sonicator probe (*see* Williams 1986 at p. 184, col. 2, last paragraph). This method results in the production of SUVs -- a result confirmed by the data in Williams 1986, Fig. 5 which shows that Williams' SUVs co-elute with the LDL fraction ("P1"), which is known to be 30 nm.

CONCLUSION

Entry of the foregoing amendments and remarks is respectfully requested. No other fee is believed to be due with this Reply. However, if any other fee is required, please charge the fee to Deposit Account No. 16-1150. In view of the above remarks and amendments, it is submitted that the presently pending claims are in form for allowance and early action to that end is requested. If any issues remain, the Examiner is requested to telephone the undersigned at (858) 314-1130.

Respectfully submitted,

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